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Evaluation of Skeletal and Extra-Skeletal Tuberculosis by FDG-PET/CT with Clinical Correlation

Ravi Shriwastav [1*], Ravi Kant Gupta [2], Ravi Mittal [1], Rakesh Kumar [2], Sagar Poudel [3], Prakash Chand Yadav [4]

[1] Department of Orthopaedics, AIIMS, New Delhi, India

[2] Department of Nuclear medicine, AIIMS, New Delhi, India

[3] Department of Community medicine, AIIMS, New Delhi, India

[4] Xi'an jiaotong university, Xian, P.R China

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***Corresponding Author:**
Dr. Ravi Shriwastav,
Shriwastav.ravi1105@gmail.com

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Conflicts of Interest
There are no conflicts to declare.

ABSTRACT

Purpose: Prospective observational study to determine the role of 18F-FDG-PET/CT in evaluation of musculoskeletal tuberculosis

Methods: 15 patients diagnosed with primary musculoskeletal tuberculosis clinico-radiologically or histopathologically underwent whole body 18F-FDG-PET/CT prior to start of ATT, after 6 and 12 months of ATT along with clinical assessment and clinical parameter (pain, swelling, tenderness and overall clinical score including these three) was compared to disease response on 18F-FDG-PET/CT **after** continuation of ATT at 6- and 12-months follow-up. Also, response of disease (both skeletal and extra skeletal lesions) was compared on subsequent follow-up on 18F-FDG-PET/CT quantitatively.

Results: After 6 months of treatment, response in pain was high however high metabolic activity persisted on 18F-FDG-PET/CT (kappa value 0.191)**.** However, when metabolic activity compared with overall clinical score, there was a fair agreement (kappa value 0.271) between these two. Similarly, when it was compared after 12 months, there were a total disagreement (kappa value - 0.024) between the responses of pain, tenderness and overall assessment with metabolic activity on 18F-FDG-PET/CT. There was significant decrease in disease activity of extra skeletal lesions after 6 months of ATT (p value 0.024) with response noted in more than 80% lesions.

Conclusion: 18F-FDG-PET/CT can detect early response and residual disease in skeletal and extra-skeletal tuberculosis in comparatively asymptomatic patient even up to 18 months treatment and can be used to modify treatment period. It has high ability to detect extra-skeletal lesions in skeletal tuberculosis and so can be used for extent of disease.

Keywords: SKELETAL TUBERCULOSIS; FDG-PET/CT IN TUBERCULOSIS; PET IN EXTRA-SKELETAL TUBERCULOSIS; CLINICAL SYMPTOMS AND PET COMPARISON IN TB; EVALUATION OF TUBERCULOSIS BY PET/CT; RESPONSE ASSESSMENT BY PET IN TB

Introduction

Tuberculosis (TB) is a chronic mycobacterial infection, with a latency period following initial infection. Bone and joint TB accounts for 2.2–4.7% of all TB cases in Europe and USA and around 10–15% of extra-pulmonary TB, whereas in developing countries, the incidence of EPTB is 15–20% [1]. Although pulmonary TB may be absent, patients may demonstrate systemic symptoms of fatigue, lethargy, and weight loss. Thus, bone and joint tuberculosis presents with pain, swelling, restricted range of motion, limp, deformity and discharging sinus with or without constitutional symptoms. Diagnosis of skeletal and articular tuberculosis is mainly clinico-radiological. However, laboratory investigations like ESR and CRP along with AFB culture and ZN stain, gene Xpert, PCR and biopsy if needed is also recommended. Radiographs may demonstrate a classic Phemister triad [2] which include juxta-articular osteopenia, joint space reduction and erosions. Histopathology will show a central necrosis surrounded by histiocytes and occasional giant cells [3]. MRI shows altered marrow signals, synovial thickening, bony erosions, soft tissue swelling and joint effusion. Unlike pulmonary TB, treatment of bone and joint TB often requires 12-18 months of chemotherapy [4].

18fluoro-fluorodeoxyglucose-positron emission tomography/computed tomography (18F-FDG-PET/CT) provides a unique and quantitative method to study tissue in vivo. It has been used successfully for imaging of cancer metabolism and for the localization of infection and inflammation based on detection of increased glucose metabolism, which in TB is mainly due to increased macrophage and neutrophil activity.

It can be used to define the extent of systemic involvement, yield material for culture and monitor the healing process. It may suggest the sites of high yield biopsies, thus yielding confirmatory histopathology and culture samples [5,6].

Materials and methods

The prospective observational study was conducted at Department of Orthopaedics and Department of Nuclear medicine, AIIMS, New Delhi from September 2017 to June 2019 with sample size of 15 patients.

All the patients of primarily skeletal and articular tuberculosis who were either clinico-radiologically diagnosed or histopathologically proven were included in the study after taking informed and written consent. However, patients with past history of antitubercular therapy (ATT) intake, uncontrolled diabetes, operated cases of TB, hypersensitivity to ATT and known case of multidrug resistant TB were excluded from the study.

Of the 15 patients, 11 (73.33%) were males and 4 (26.66%) were females with mean age 37.5 years and age range 13-60 years. The commonly affected sites were ankle joint (n=7) followed by knee joint (fig.1a,1b) (n=5)

and then elbow (fig.4a,4b) (n=2) and wrist joint (n=1). 11 patients (73.33%) showed features of tuberculosis on histopathology. Only 2 patients (13.33%) showed positive GeneXpert test. However, rapid culture and PCR were negative in all 15 patients (Table 1).

Table 1: Demographic details of patients with primary bone and joint TB

Demographic details of all patients (n = 15)		
Sex	Males	11
	Females	4
Joints affected	Ankle	7
	Knee	5
	Elbow	2
	Wrist	1
HPE evaluation	Biopsy proven TB	11
	Clinico-radiologically proven TB	4
Other microbial tests and modalities	Gene Xpert Positive	2
	Culture positive	0
	PCR positive	0
Constitutional symptoms	At the time of diagnosis	10
Extra skeletal involvement on PET/CT	Lymph nodes	15
	Lungs	7
	Vertebra	3
	Pleura	1

Clinical assessment of musculoskeletal TB followed by X-ray (AP and lateral views) and MRI of the affected part was done. On the background of clinico-radiological diagnosis, tissue biopsy was done for histopathology along with rapid culture sensitivity, GeneXpert and PCR tests. Prior to start of ATT (2HRZE + 16HR), 18F-FDG-PET/CT was done to analyse the disease activity and extent of disease. Follow-up scans along with clinical evaluation were done after 6 months± 1 week and 12 months± 1 week of ATT to evaluate the treatment response.

Pain was assessed using visual analogue scale (VAS score). The degree of joint tenderness was measured as (0-no pain, 1-mild pain, 2-wincing pain, 3-withdrawl on palpation) and joint swelling was measured with reference

to circumference of the joint as (0-no swelling, 1-mild swelling, 2-moderate swelling, 3- gross swelling filling joint line) [7]. Decrease of at least 50% or more in pain score, any decrease in score of tenderness and swelling and 50% or more decrease in total score (adding all 3 scores) on follow-up was regarded as clinical response to therapy.

All the patients underwent 18F-FDG-PET/CT at 0 and after 6 and 12 months of ATT. PET images were looked for the area of increased radiotracer uptake. For semiquantitative analysis, a region of interest (ROI) was carefully drawn around the site of the abnormal uptake in the consequent 4 to 6 18F-FDG-PET/CT slices. The slice with a maximal uptake in the ROI was chosen for quantitative measurement of metabolic activity of the tracer, i.e. maximum standard uptake value (SUVmax). From these ROIs, the SUVmax was calculated.

In all patients, in addition to serial SUVmax values, lesion to background ratio was taken. Liver was taken as background in whole body images. If not available, background was obtained from contralateral non active homogenous muscle.

The ratio of SUVmax of target lesion to the SUVmax of background was calculated and it was used for response evaluation to avoid errors related to time, body weight calculation and injected dose accuracy.

For primary skeletal and articular tuberculosis lesions, lesion showing metabolic activity more than 2.5 times the background metabolic activity was considered positive for tubercular involvement i.e., infective. After 6 months and 12 months of ATT, if the ratio of SUVmax and background SUVmax of a particular lesion was less than or equal to 2.49, it was considered as response to ATT. However, for other lesions (lesions other than primary skeletal and articular tuberculosis lesions) - more than 1.49 times the background metabolic activity was considered positive for tubercular involvement i.e., infective. However, if the ratio was less than or equal to 1.49 (lesser than considered threshold SUVmax), it was considered as uninvolved lesion (negative).

All the lesions showing increased metabolic activity were noted. SUVmax was calculated for that particular lesion and was compared to the background SUVmax. The ratio of SUVmax of lesion and background SUVmax was calculated for the lesion. Same procedure was repeated after 6 and 12 months follow-up scans. The ratio at baseline was compared to the ratio at 6 months and 12 months to see for response and resolution of lesions. The ratio at baseline was compared to clinical score at baseline, the ratio at 6 months was compared to clinical score at 6 months follow-up and the ratio at 12 months was compared to clinical score at 12 months follow-up. Then statistical analysis of clinical score and SUVmax ratio between 0 and 6 months (0-6) and 0 and 12 months (0-12) was done so as to co-relate the response between clinical finding and 18F-FDG-PET/CT. Statistical analysis was done using cohen's kappa statistics and strength of agreement was calculated based on kappa value (<0.2: poor, 0.21-0.40: fair, 0.41-0.60: moderate, 0.61-0.80: good, 0.81-1.00: very good agreement). Statistical analysis of SUVmax ratios of 18F-FDG-PET/CT at 3 intervals (0, 6 & 12 months) was done using chi-square test and P value <0.05 with 95% CI was considered significant.

Figure Legends:

42-year male presented with pain & swelling of right knee for 3 months, associated with history of evening rise of fever & wt loss. X-ray and MRI of right knee was done. ESR and CRP were raised. Clinico-radiologically he was diagnosed with tuberculosis of right knee. Synovial biopsy was suggestive of TB. Baseline 18F-FDG-PET/CT showed metabolically active disease involving right knee joint (fig.1a, 1b) with bilateral lungs lesions (fig.1c). Metabolic response of bilateral lung nodules was seen after 6 months (fig 2c) & 12 months (fig 3c) of therapy. However metabolic activity persisted at the end of 12 months in the region of knee joint lesion (fig. 3a, 3b) suggestive of residual disease.

25-year male presented with pain & swelling of right elbow for 2 months. There was no history of evening rise of fever & wt loss. X-ray and MRI of right elbow was done. ESR and CRP were raised. Clinico-radiologically he was diagnosed with tuberculosis of right elbow. Synovial biopsy suggested TB on histopathology. Baseline 18F-FDG-PET/CT showed metabolically active disease involving right elbow (fig.4a, 4b) with involvement of ipsilateral axillary lymph nodes (fig 4c). There was metabolic resolution of axillary lymph node after 6 months of ATT (fig 5c) with mild metabolic activity in right elbow lesion (fig 5a,5b). There was minimal metabolic activity persisted after 12 months in the region of right elbow (fig. 6a, 6b) suggestive of residual disease.

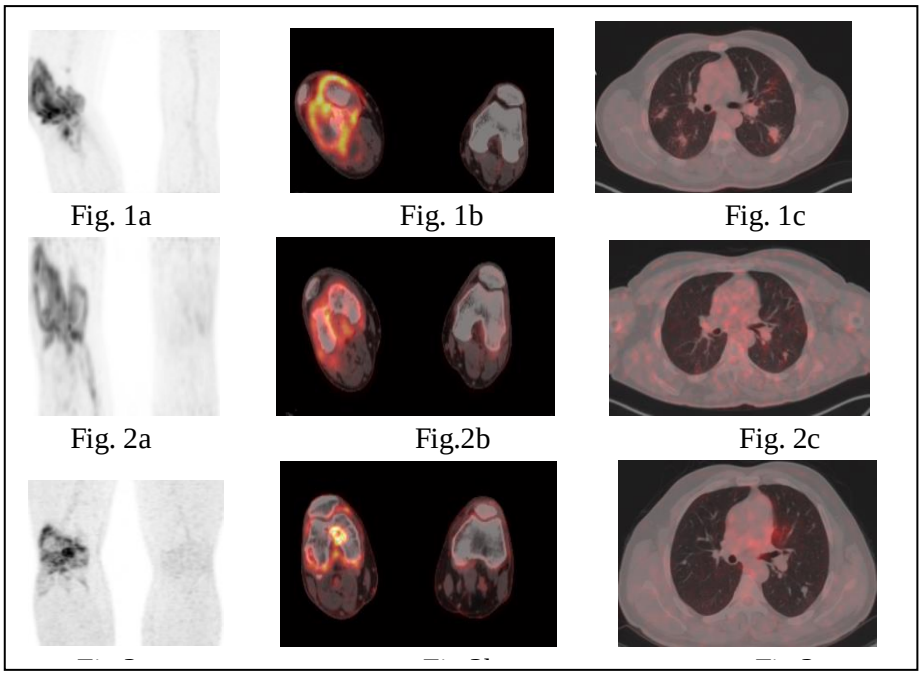

Fig. 1a Fig. 1b Fig. 1c

Fig. 2a Fig.2b Fig. 2c

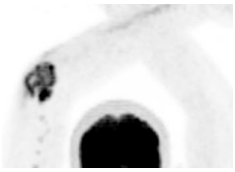

Fig. 4a

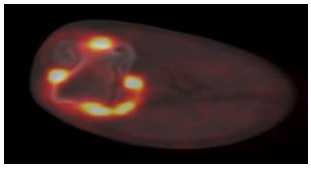

Fig. 4b

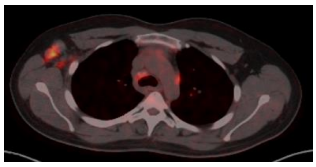

Fig. 4c

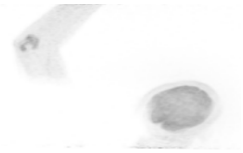

Fig. 5a

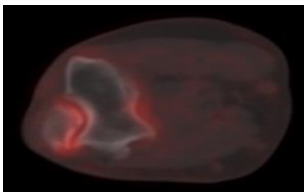

Fig.5b

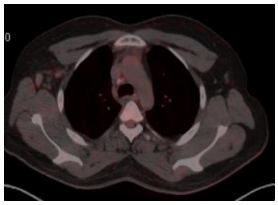

Fig. 5c

Fig 6a

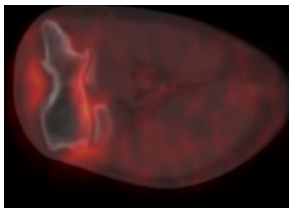

Fig 6b

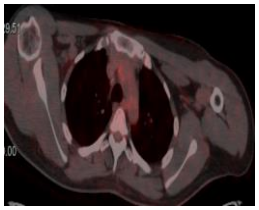

Fig.6c

Results

All 15 patients (100%) had involvement of lymph nodes (fig.4c), 7 patients (46.6%) had pulmonary involvement (fig 1c), 3 patients (20%) had vertebral tuberculosis and 1 patient (6.6%) had pleural involvement which was detected 18F-FDG-PET/CT (Table 1). There were total of 177 lesions showing increased metabolic activity, out of which 40 lesions were primarily skeletal and articular tuberculosis lesions. Prior to start of ATT, the mean SUVmax was 26.5 (4.6-59.8) which decreased down to 8.9 (2.27-28.6) after 12 months of therapy.

COMPARISON OF CLINICAL SYMPTOM AND 18F-FDG-PET/CT AT 6 MONTHS

Clinical scores (pain, tenderness, swelling and overall score) were separately compared to response of disease on 18F-FDG-PET/CT after 6 months of ATT. 40 musculoskeletal lesions showed increased metabolic activity at the time of diagnosis on 18F-FDG-PET/CT. After 6 months of ATT, 17 lesions out of 40 showed response and 23 were stable. The response in 18F-FDG-PET/CT was compared with pain, swelling, tenderness and overall clinical score.

Among total 40 lesions, 35 lesions showed response in pain and 5 were stable. For 17 lesions, there was an agreement showing response in pain score and on 18F-FDG-PET/CT both. Similarly, 5 lesions showed agreement for being stable in pain score and on 18F-FDG-PET/CT both. However, rest of the 18 lesions, there was a disagreement between response in pain score and 18F-FDG-PET/CT as these lesions were stable on 18F-FDG-PET/CT but were showing response in pain scale. Using cohen's kappa statistics, kappa value (Pain vs

18F-FDG-PET/CT) was 0.191 i.e., <0.2 showing poor agreement between the responses of pain and 18F-FDG-PET/CT.

All 40 lesions showed response in tenderness and swelling after 6 months of therapy.

18F-FDG-PET/CT was compared with overall clinical score. 33 lesions out of 40 showed responses in overall clinical score and 7 were stable. For 17 lesions, there was an agreement showing overall response and on 18F-FDG-PET/CT both. Similarly for 7 lesions, there was an agreement showing stable in overall response and on 18F-FDG-PET/CT both. However, for 16 lesions, there was a disagreement showing response in overall clinical assessment but stable on 18F-FDG-PET/CT. Using cohen's kappa statistics, kappa value (overall clinical response vs 18F-FDG-PET/CT) was 0.271 i.e., between 0.2-0.4 showing fair agreement between overall clinical response and 18F-FDG-PET/CT (Table 2).

COMPARISON OF CLINICAL SYMPTOM AND 18F-FDG-PET/CT AT 12 MONTHS

Among total 40 musculoskeletal lesions with increased metabolic activity at the time of diagnosis on 18F-FDG-PET/CT, 24 lesions showed response and 16 were stable.

In pain scoring, 37 lesions out of 40 showed responses in pain and 3 were stable. So, by comparing 18F-FDG-PET/CT and pain score, it was found that 22 lesions among these were in agreement of showing response in pain and on 18F-FDG-PET/CT both. Similarly, 1 lesion was in agreement in pain response and on 18F-FDG-PET/CT both for being stable. Among rest of 17 total remaining disagreement lesions, 15 lesions were showing response in pain score but stable in 18F-FDG-PET/CT and 2 lesions were showing response in 18F-FDG-PET/CT score but stable in pain score. Using cohen's kappa statistics, kappa value (Pain vs 18F-FDG-PET/CT) was -0.024 (i.e., <0.00) was suggestive of high disagreement between the responses of pain and 18F-FDG-PET/CT.

In tenderness analysis, among total 40 lesions 22 lesions were showing response. Out of 16 stable lesions on 18F-FDG-PET/CT, 15 responded in tenderness. 1 lesion was stable on both 18F-FDG-PET/CT and clinical assessment after 12 months of therapy. Using Cohen's kappa statistics, kappa value (tenderness vs 18F-FDG-PET/CT) was -0.024 i.e., <0.00 showing disagreement between the responses of tenderness and 18F-FDG-PET/CT.

On swelling score analysis, all 40 lesions had response in swelling.

On assessment with overall clinical score, 37 lesions out of 40 showed responses in overall clinical score and 3 were stable. For 22 lesions, there was an agreement showing overall clinical response and on 18F-FDG-PET/CT. Similarly for 1 lesion, there was an agreement showing stable in overall clinical score and on 18F-FDG-PET/CT. For 15 lesions, there was a disagreement showing response in pain but stable on 18F-FDG-PET/CT and 2 lesions where disagreement showed response on 18F-FDG-PET/CT but stable in pain. Using cohen's kappa statistics, kappa value (overall clinical score vs 18F-FDG-PET/CT) was -0.024 i.e., <0.00 showing disagreement between overall clinical response and 18F-FDG-PET/CT (Table 2).

Table 2: Evaluation of response of disease after antitubercular therapy (clinical response i.e., pain, swelling, tenderness and overall assessment versus 18F-FDG-PET/CT) at 6 months and 12 months

Response evaluation of disease after ATT	Comparison	Kappa value	Comments
Response between 0 and 6 months	Pain VS 18F-FDG-PET/CT	0.191	Poor agreement between response in pain and response of disease on 18F-FDG-PET/CT
	Tenderness VS 18F-FDG-PET/CT	-	Clinical response in tenderness seen in all patients
	Swelling VS 18F-FDG-PET/CT	-	Clinical response in swelling seen in all patients
	Overall clinical response VS 18F-FDG-PET/CT	0.271	Poor agreement between response in overall clinical score and response of disease on 18F-FDG-PET/CT
Response between 0 and 12 months	Pain VS 18F-FDG-PET/CT	-0.024	Total disagreement between response in pain and response of disease on 18F-FDG-PET/CT
	Tenderness VS 18F-FDG-PET/CT	-0.024	Total disagreement between response in tenderness and response of disease on 18F-FDG-PET/CT
	Swelling VS 18F-FDG-PET/CT	-	Clinical response in swelling seen in all patients
	Overall clinical response VS 18F-FDG-PET/CT	-0.024	Total disagreement between response in overall clinical score and response of disease on 18F-FDG-PET/CT

RESPONSE ASSESSMENT ON THE BASIS OF 18F-FDG-PET/CT

There was total 177 lesions on 18F-FDG-PET/CT prior to therapy. Among them 40 lesions were skeletal and articular and 137 were extra-articular lesions.

RESPONSE ON 18F-FDG-PET/CT AT 6 MONTHS

In skeletal and articular lesions: 17 (42.5%) lesions out of total 40, showed response after 6 months of therapy. However, 23 (57.5%) lesions were marked persistent disease.

In extra-articular lesions: 110 lesions (80.29%) were positive at baseline. There were only 26 lesions (18.98%) which remained positive after 6 months of ATT (Table 3).

RESPONSE ON 18F-FDG-PET/CT AT 12 MONTHS

In skeletal and articular lesions: 24 lesions (60%) out of total 40, showed response after 12 months of therapy. This includes 17 responded lesions of 6 months with additional 7 lesions.

In extra-articular lesions: Only 23 lesions (16.79%) were positive after 12 months of therapy (Table 3).

Table 3: Positive and negative extra skeletal lesions at baseline and after 6 and 12 months of ATT

Lesions	Before ATT	6 months of ATT	12 months of ATT
Negative	27 (19.71%)	111 (81.02%)	114 (83.21%)
Positive	110 (80.29%)	26 (18.98%)	23 (16.79%)
Total	137 (100%)	137 (100%)	137 (100%)

COMPARISON OF RESPONSE AT 6 AND 12 MONTHS FOR SKELETAL AND ARTICULAR LESIONS

After 6 months of therapy, 17 out of 40 lesions were showing response to treatment. By the end of 12 months of therapy, it was 24. Among 17 lesions, which showed response at the end of 6 months of therapy, 15 lesions showed further response to therapy at the end of 12 months. However, remaining 2 lesions among 17 were stable at the end of 12 months.

There were 23 stable lesions at the end of 6 months of therapy. Among these 23, 14 lesions remained stable even after 12 months of therapy. However, remaining 9 lesions showed response after 12 months of therapy.

SUVmax ratio at 6 months was compared with that of 12 months and p value was found to be 0.002 showing significant decrease in Metabolic activity after 12 months of ATT (Table 4).

Table 4: Comparison of SUVmax ratio of primary skeletal and articular tuberculosis lesions at 6 and 12 months

Response evaluation	**SUVmax ratio at 12 months (R2)**		**Total**
SUVmax ratio at 6 months (R1)	Lesions	Negative	Positive
	Negative	15 (62.5%)	2 (12.5%)	17 (42.5%)
	Positive	9 (37.5%)	14 (87.5)	23 (57.5%)
Total		24 (100%)	16 (100%)	40 (100%)

EXTRA-ARTICULAR LESIONS: RESPONSE AFTER 6 MONTHS OF THERAPY

Among 137 extra-articular lesions, 110 lesions were assigned positive and 27 lesions were assigned negative on the basis of SUVmax ratio threshold.

After 6 months of ATT among total 110 positive lesions, 85 lesions became negative but 25 remained positive. Among 27 negative lesions, 26 remained negative after 6 months. However, one of the 27 negative lesions at baseline, started showing high SUVmax ratio after 6 months of therapy, and so was assigned positive.

The outcome at 6 months was compared with baseline values. There was significant decrease in metabolic activity of extra-articular lesions at 6 months of therapy (p value – 0.024; 95% CI) (Table 5).

Table 5: Comparison of SUVmax ratio of extra skeletal lesions at 0 and 6 months

Response evaluation	**SUVmax ratio at 6 months (R1)**		**Total**
SUVmax ratio at baseline (R0)	Lesions	Negative	Positive
	Negative	26 (23.42%)	1 (3.85%)	27 (19.71%)
	Positive	85 (76.58%)	25 (96.15%)	110 (80.29%)
Total		111 (100%)	26 (100%)	137(100%)

EXTRA-ARTICULAR LESIONS: RESPONSE AFTER 12 MONTHS OF THERAPY

After 12 months of ATT among total 137 positive lesions, 114 lesions became negative but 23 remained positive for disease. There were 103 lesions which were negative and 15 lesions which were positive after 6 and 12 months of ATT both. 8 lesions which were negative after 6 months showed positive after 12 months. However, 11 lesions which were positive after 6 months became negative after 12 months of therapy. SUVmax ratio at 6 and 12 months was compared and P value was found to be <0.05 showing significant decrease in metabolic activity after 12 months of therapy (Table 6).

Table 6: Comparison of SUVmax ratio of extra skeletal lesions at 6 and 12 months

Response evaluation	**SUVmax ratio at 12 months (R2)**		**Total**
SUVmax ratio at 6 months (R1)	Lesions	Negative	Positive
	Negative	103 (90.35%)	8 (34.78%)	111 (81.02%)
	Positive	11 (9.65%)	15 (65.22%)	26 (18.98%)
Total		114 (100%)	23 (100%)	137(100%)

Being an observational study, ATT was continued for 18 months. According to 18F-FDG- PET/CT, they were classified into two groups, patient with residual disease and patients with complete metabolic response. 2 patients from each group were able to complete their 18 months of ATT within the study period and underwent 18F-FDG- PET/CT at the end of 18 months. The patients from complete metabolic response group remained with all lesions in negative state (SUVmax ratio for skeletal lesions < 2.49 and extra skeletal lesions were <1.49). The lesions which were positive of other two patients from partial response group at 12 months of therapy showed further decrease in metabolic activity, and became negative at 18 months of therapy.

The mean value of scores of pains, tenderness and swelling was 6.6 (SD 1.58 and range 3-9), 2.26 (SD 0.44 and range 2-3) and 2.53 (SD 0.49 and range 2-3) respectively before the start of antitubercular therapy. After 6 months of ATT, mean value of pain, tenderness and swelling decreased to 2.53 (SD 1.58 and range 0-6), 0.93 (SD 0.44 and range 0-2) and 1.13 (SD 0.80 and range 0-2) respectively which further decreased to 0.93 (SD 0.85 and range 0-2), 0.53 (SD 0.61 and range 0-2) and 0.53 (SD 0.61 and range 0-2) after 12 months. At the time of diagnosis before starting ATT, 10 patients (66.66%) had constitutional symptoms which resolved within 2 months of ATT.

Discussion

In our study, we analyzed the role 18F-FDG- PET/CT in diagnosis and monitoring treatment response in cases of musculoskeletal tuberculosis. In coming days, it can be used along with other modalities for early diagnosis and monitoring treatment response with simultaneous detection of pulmonary and extrapulmonary involvement. The most commonly affected site for skeletal and articular tuberculosis in our study was ankle joint followed by knee, elbow and wrist. However, in a study conducted by Golden M et al (2005), articular TB was more commonly found in hip and knee (90%) and also chest X-ray showed pulmonary tuberculosis in 33-50% cases [8]. Out of 15 patients, 7 patients (46.6%) also had pulmonary involvement and 3 patients (20%) had vertebral involvement which was detected on 18F-FDG-PET/CT. 11 patients (73.3%) showed features of tuberculosis on histopathology.

Among 40 skeletal and articular lesions with increased metabolic activity, there was gradual decrease in metabolic activity after continuation of ATT with mean SUVmax 26.5 (4.6-59.8) prior to start of ATT which decreased down to 8.9 (2.27-28.6) after 12 months of therapy. In a study by Liu et al (2013), out of 88 cases which also included 28 cases of osteoarticular TB showed high metabolic activity with SUVmax max ranging from 1.3-23.2 [9] which is low compared to our study. One reason for higher SUVmax values in our study could be the delayed presentation of patients with initial diagnostic dilemmas and high disease burden.

In our study, there was poor agreement (kappa value 0.191) between pain response and response of disease on 18F-FDG-PET/CT and fair agreement (kappa value 0.271) between overall clinical score and response of disease on 18F-FDG-PET/CT after 6 months of therapy. However, there was a total disagreement (kappa value -0.024) between the responses of pain, tenderness and overall assessment and response of disease on 18F-FDG-

PET/CT after 12 months of ATT intake. Clinical response occurs within months but metabolic activity of the lesions take time to resolve on 18F-FDG-PET/CT. In a study by Paus (1964) and Kaplan (1959) on relapse of osteoarticular TB, relapse rates reported were 11 and 2% respectively and nearly 50% cases with recurrence did not continue drugs for more than 12 months. This is a strong pointer against accepting "short course chemotherapy" for osteoarticular tuberculosis. However, precipitating factors for relapse may be lowered nutritional status or compromised immune state. This is strong evidence supporting the persistence of metabolic activity in 40% of musculoskeletal lesions on 18F-FDG-PET/CT in our study after 12 months (fig.3b, 6b) of ATT even though patients were asymptomatic.

Also, the evidence of non-infectivity of unhealed skeletal lesions at 12 months after the 4th 18F-FDG-PET/CT after 18 months of ATT is a strong indicator of requirement of long-term chemotherapy in cases of musculoskeletal TB. Index-TB guidelines advocates the use of extended course of chemotherapy with an intensive phase of 2 months (2 HRZE) and continuation phase of 10-16 months (10/16 HRE) depending on site of disease and patient's clinical course. This is in support to our finding on 18F-FDG-PET/CT for the need of continuation of ATT after 12 months even after clinical resolution of symptoms. Also, the response of ATT on 18F-FDG-PET/CT for extra skeletal lesions within 6 months (fig.2c,5c) is much better than that of skeletal lesions (> 80% lesions negative) which supports the short-term chemotherapy regimen (Index-TB guideline- 6 months) for pulmonary and lymph node TB.

Conclusion

18F-FDG-PET/CT can be used to find the extent of systemic involvement of skeletal and articular tuberculosis and evaluation/quantification of disease activity of both skeletal and extra skeletal TB with response to ATT. Clinical resolutions of symptoms is earlier than metabolic resolution of lesions supporting the need of 18F-FDG-PET/CT in monitoring response of therapy.

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